REMARKS

The Rejections under 35 U.S.C. §103

The rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 under 35 U.S.C. §103, as being obvious over the combination of Nishimura (Allergology) and Banholzer (U.S. Patent No. 5,610,163), and the rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 under 35 U.S.C. §103, as being obvious over Keller (WO 00/28979, corresp. to U.S. Patent No. 6,645,466), Nishimura and Banholzer in combination, are respectfully traversed.

Applicants maintain their position that neither combination of reference teachings creates a prima facie case for obviousness of the claimed invention. Applicants also maintain their position that the previously submitted Declaration under 37 C.F.R. §1.132 provides further clear and convincing evidence of the nonobviousness of the claimed invention.

In the current Office action, it is agreed that a showing of synergism can overcome a prima facie case for obviousness. However, the Office action appears to contradict this agreement by then stating that applicants showing is not persuasive because it lacks a comparison to the prior art composition. Applicants again submit that the law is clear that a showing of synergism – alone – can be sufficient to prove nonobviousness. The PTO's own manual, at MPEP §716.02(a)(I), makes clear that a showing of synergism alone can be sufficient proof of nonobviousness, stating:

> Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

The law and PTO practice make clear that there is more than one way to prove nonobviousness. See also In re Soni, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), confirming that "all evidence of nonobviousness must be considered when assessing patentability" and finding nonobviousness based on data showing an unexpected advantage from a showing of properties rather than from a direct comparison of the prior art. See also American Hoist and Derrick Co. v. Sowa & Sons, 220 USPQ 763, 771 (Fed. Cir. 1984), supporting that the existence of an

unexpected result **or** a synergistic effect may support nonobviousness. Thus, while a direct comparison to the closest prior art composition (presumably the Nishimura composition since it is the only specific embodiment in the prior art which combines two actives) is one way to prove nonobviousness, the absence of such a direct comparison does not preclude applicants from proving nonobviousness in other ways, i.e., with the showing of synergism. Applicants urge that this point of law and practice be properly acknowledged and applied.

Applicants' showing of the synergistic effect of their specific combination provides – on its own -- a clear and convincing showing of unexpected properties of the claimed invention. It is alleged in the Office action that applicants must show that the unexpected advantages also provide a significant and practical advantage. Applicants, however, have clearly provided this and the Office action does not address the arguments applicants made on this point in the previous reply. As for the significance of the synergistic advantage, this should be self-evident from the data and graphically shown in the graph attached to the declaration. For example, the declaration shows that the bronchoprotective effect of the ciclesonide 0.1 mg/kg was 5% at 3 hours and 5% at 24 hours and the bronchoprotective effect of the tiotropium bromide 0.06 mg/kg was 35% at 3 hours and 12% at 24 hours. Their combination, however, according to the invention, provided bronchoprotection of 49% at 3 hours and maintain 41% bronchoprotection after 24 hours. Thus, the sustained bronchoprotection effect for the claimed combination was **more than twice** that of the added effect of the two components separately. This is a highly significant advantage. As for the practicality of the effect, it should be self-evident that the observed surprising bronchoprotective effect is highly practical for using the combination in treating respiratory diseases. The specification as a whole supports that the bronchoprotective activity -- which is shown to be synergistically advantageous for applicants' specific combination -- makes the compounds useful for treating such diseases; see, e.g., page 1, lines 16-23, and page 4, lines 5-13, of the instant specification. The PTO has provided no evidence or reasoning to suggest that the advantages shown by applicants' are not significant or practical.

It is alleged in the Office action that applicants cannot compare the results obtained in humans (Nishimura) with that obtained in laboratory animals (dogs in applicants' data). However, applicants have not done this. The showing of synergism is only from the comparison

of applicants' own data in dogs. The comparison is of the combination composition according to the invention versus the additive effect of the components separately. This is how synergism is proven. There is no comparison to Nishimura. Applicants arguments about Nishimura (as detailed below) are that it fails to suggest a synergistic effect of the combination.

The record makes clear that the significant and practical synergistic advantage shown for applicants' combination is unexpected from the cited prior art. There are no teachings in the prior art from which one of ordinary skill in the art would expect that the combination of tiotropium and ciclesonide could provide an effect significantly greater than their additive effect, certainly not more than twice the additive effect. The teachings of Nishimura regarding the oxitropium/beclamethasone combination certainly provide no such expectation. To the contrary, Nishimura itself indicates that the addition of the oxitropium to beclamethasone provided only a "small improvement" in treatment; see the concluding discussion on pg. 87. None of the cited prior art references give any suggestion that a combination of an anticholinergic and a corticosteroid would be expected to result in a synergistic advantageous property.

It is alleged in the Office action that applicants' showing is not persuasive "because it does not show the results are greater than those expected from the prior art." Applicants strongly disagree. Applicants have shown that the sustained bronchoprotection effect for the claimed combination was **more than twice** that of the added effect of the two components separately. This is clearly unexpected over the Nishimura teachings. From Nishimura and the other references, one of ordinary skill in the art could not have expected more than just an additive effect from a combination of anticholinergic and steroid. Applicants show an effect more than double the additive effect. Applicants request an explanation of how such a dramatic synergistic advantage could have been expected from the cited prior art. It is true that Nishimura teaches combining oxitropium bromide and beclomethasone (just this specific combination). But neither this teaching, nor the teachings in Banholzer and Keller, give any hint that the combination of the different anticholinergic, tiotropium, and different steroid, ciclesonide, would provide a significantly higher than additive effect. This synergistic effect is unquestionably unexpected.

As a result, applicants urge that the position taken in the Office action, i.e., that the synergistic effect of the claimed invention demonstrated by applicants is not unexpected, is not

supported on the record. To the contrary, the Nishimura reference itself makes clear that the combination taught therein does not provide any significant additive or synergistic effect. There are no teachings in the prior art from which one of ordinary skill in the art would have an expectation that the combination of tiotropium and ciclesonide could provide an effect significantly greater than their additive effect. The teachings of Nishimura regarding the oxitropium/beclamethasone combination certainly provide no such expectation. To the contrary, Nishimura itself indicates that the addition of the oxitropium to beclamethasone provided only a "small improvement" in treatment; see the concluding discussion on pg. 87. None of the cited prior art references give any suggestion that a combination of an anticholinergic and a corticosteroid would be expected to result in a synergistic advantageous property.

Considering the record as a whole, applicants urge that they have provided clear and convincing evidence of significant and practical advantages of their particular combination. Further, they have shown that these advantages were unexpected in view of the prior art teachings. The prior art gives no hint to one of ordinary skill in the art that the specific combination of the specific anticholinergic, tiotropium salt, and the specific corticosteroid, ciclesonide, would be particularly advantageous. Thus, a clear and convincing showing of nonobviousness is provided by the showing of synergism. For this reason alone, the obviousness rejections should be withdrawn.

Further, applicants submit that the references fail to establish a prima facie case of obviousness or, at most, only a weak case which is readily overcome by the Declaration, for the following reasons.

Nishimura discloses the use of a combination of oxitropium bromide with a certain inhaled corticosteroid, i.e., beclomethasone diproprionate, for use in treating chronic asthma. Nishimura alleged that the combination of the oxitropium bromide provided advantages over beclomethasone diproprionate alone. But the advantages are only minor and there is no allegation or proof that the advantages are more than merely the additive effect.

Banholzer discloses a generic formula (I) encompassing a range of compounds which includes tiotropium salts. Claim 5 is directed particularly to tiotropium salts.

Keller discloses adding magnesium stearate to powder formulations to improve their

moisture resistance; see, e.g., col. 4, lines 16-25. Keller teaches that its invention can be applied to powders containing a wide variety of active agents and includes tiotropium and ciclesonide as examples of possible actives; see, e.g., col. 6, line 13, to col. 7, line 10. Keller also provides a general discussion of possible excipients which include some of the ones listed in the current claims; see, e.g., col. 8, lines 1-16. However, Keller provides no suggestion to specifically combine tiotropium, ciclesonide and one of the specific excipients recited in the current claims. Further, Keller certainly provides no hint that such a combination would provide unexpected synergistically advantageous properties, as shown by applicants.

The basis for the rejections is that it would have been obvious to one of ordinary skill in the art to exchange the oxitropium bromide of Nishimura with the tiotropium compound disclosed in Banholzer. However, such a combination would not meet or suggest the elements of the claims and, thus, not support a prima facie case of obviousness. The instant claims recite a combination of the tiotropium compound and the particular steroid, ciclesonide. None of the references provide any suggestion to combine the particular steroid ciclesonide. Nishimura discloses only a beclomethasone salt, Banholzer provides no teachings regarding any steroid and Keller provides no teaching to specifically combine tiotropium and ciclesonide. The combined reference teachings thus fail to meet this claim element. The instant claims further recite, in addition to the tiotropium compound and the ciclesonide compound, "a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose." None of Nishimura, Banholzer or Keller provide any teaching regarding a composition containing such a particular excipients with the particular combination of tiotropium and ciclesonide. Further, the Office action provides no reasoning as to why a composition including this specific combination of elements would be obvious to one of ordinary skill in the art.

For these additional reasons, i.e., the weakness of the prima facie showing, the combined references in view of the evidence of nonobviousness fail to support the obviousness rejection. It is urged that the cited prior art, considered as a whole on the record, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejections under 35 U.S.C. §103 should be withdrawn.

It is submitted that the application is in condition for allowance. But the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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